Study Title: BRE 18108: A pilot of feasibility neoadjuvant study of a 2-week ketogenic diet in combination with letrozole to modulate PI3K signaling in ER+ breast cancer

Version Date: 20JUL2022 **PI:** Brent Rexer, MD, PhD NCT03962647

Name of participant:_____ Age:_____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

What is the purpose of this study?
You are being asked to take part in this research study because you have been diagnosed with early stage operable breast cancer and have a body mass index (BMI) of 30 or more. The type of cancer you have has special proteins on it, called estrogen receptors (ER), that allow it to grow when exposed to estrogen. The purpose of this study is to learn if the combination of a 2 week ketogenic (low calorie, low carbohydrate) diet in combination with letrozole (Femara®) can help slow the growth of tumors. The hope is that the ketogenic diet will normalize abnormally high insulin levels that in turn will slow the growth of cancer cells. Letrozole (Femara®) is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer and is a type of drug called an aromatase inhibitor (AI). We plan to enroll 36 participants at Vanderbilt in this study.

How the Study Drugs are Given?
If you agree to joint in this study, you may get either letrozole alone, or letrozole plus a diet that is lower in calories and lower in carbohydrates than a typical diet.
If the screening tests show you can be in the study, then you will be asked to return to the cancer clinic for your first visit. A computer will decide whether you will go into the diet plus letrozole group or the letrozole only control group. This process is called "randomization," like flipping a coin to decide on a group. You and your doctor will be told which treatment you are assigned. For every 2 patients in the diet plus letrozole group, one patient will go to the letrozole only group.
You will be given a prescription for letrozole after screening assessments are completed and you are eligible to be in this protocol.

Side effects and risks that you can expect if you take part in this study:
Letrozole Risks
Common side effects you might have from Letrozole include:

- Joint pain
- Hot flashes/Flushing

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Letrozole is a standard treatment for your type of breast cancer, whether or not you participate in this study. You should discuss with your doctor if you have any other possible side effects while taking letrozole. Letrozole side effects can be reversed, if they occur, when you stop taking the drug.

Diet Risks

If you are randomized to the diet arm of this study, you will start a diet that is lower in calories and lower in carbohydrates than a typical diet. The side effects you may experience on this diet include:

- Hunger
- Dizziness
- Dry mouth
- Headache
- Bad breath
- Fatigue
- Weakness
- Muscle cramps
- Constipation

Hunger is usually most severe the first 2-3 days of the diet. Dizziness and weakness can be helped by drinking more fluids and sometimes more salt intake. Muscle cramps can be helped by replacing minerals (potassium or magnesium). You will be monitored during the diet for these side effects and for the level of electrolytes in your body.

Biopsy Risks (if performed)

If you do not proceed with surgery for your breast cancer at the end of the study (this would be unusual), your study doctor may ask if you would be willing to undergo a breast biopsy. Your study doctor and the biopsy doctor will explain the procedure to you before it is performed. Biopsy risks can include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.
- You may receive an injection of lidocaine to numb the area of the biopsy site. Lidocaine, a numbing drug, may burn or cause a rash, redness, or soreness where you get the shot. There is a risk that this drug may cause problems with heart rhythm.

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- Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Risks that are not known:
Because this treatment is investigational, meaning not standard of care, there may be risks that we do not know about at this time.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study:
This research may contribute to understanding of cancer and its treatment and may eventually lead to improvements in treatment. This research may also help to increase our understanding of how obesity affects breast cancers.

There may or may not be a direct benefit to you as a result of your participation in this study. You may lose a little bit of body weight during the course of the study. There may be other treatment options that are available to you, including receiving standard therapies. You should speak to your doctor about all of your treatment options prior to deciding to participate in this study.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Procedures to be followed:
Many of the procedures listed below are part of your routine care. Any tests or procedures that are not considered part of your routine care will have 'research only' written next to it. If you give your consent to be in this study by signing this form, you will have tests and procedures (called "screening") done.

SCREENING:

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Before treatment starts, you will undergo a screening process. Most of this screening process is done on all cancer patients whether or not they are taking part in a study. After you have signed this consent, the screening tests listed below will be done within 60 days of your first study day.

- Your demographics (for example, age, race, and gender) will be reviewed
- Complete medical history, including any problems you may be having and a list of all medications you are taking (including prescriptions, over the counter medications, herbal medications, and vitamins)
- Complete physical exam
- Vital signs (height, weight, calculation of Body Mass Index (BMI), temperature, blood pressure, pulse, breathing rate, and oxygen levels in your blood)
- Blood will be drawn (about 1 teaspoon) to check your current health status, if you have not already had blood tests performed within 120 days prior to starting the study **(research only)**
    - We may also need to check hormone levels to make sure you are post-menopausal (i.e., you have "gone through the menstrual changes") **(research only)**
- Your study doctor will provide you with a prescription for Letrozole, the standard of care drug for your cancer treatment
- Request a section of your tissue from your previously collected breast biopsy **(research only)**

If you qualify for the study, you will be randomized to one of two groups: one group will receive letrozole alone. The other group will receive letrozole and will start the study diet. There is a 2 to 1 chance that you will be randomized to the diet group.

ON-STUDY VISIT– DIET INTERVENTION GROUP:

If you meet all of the screening requirements, you will return to the study clinic for your On-Study Visit. During this visit, you can expect the following procedures to be done:

- Review of medical history and medications since screening **(research only)**
- Physical exam (including vital signs, weight, and height) **(research only)**
- You will take 2.5 mg of letrozole by mouth at the same time every day for the duration of the study.
- Fasting blood work (about 1 teaspoon) will be drawn to check your health **(research only)**
- Waist measurements **(research only)**
- Fasting blood work (about 3 teaspoons) will be drawn to measure additional health factors like your blood sugar, cholesterol and insulin levels **(research only)**
- Urinalysis **(research only)**
- Perceived Stress Scale **(research only)**

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- PROMIS-29 Questionnaire **(research only)**
- You will start using the meal replacement shakes, which you will use to substitute for your regular diet for the duration of the study. You will be allowed to consume 4-5 shakes per day, and may eat plain non-starchy vegetables for the desire to chew. You will also be instructed to consume a regular lean protein plus vegetables meal for each day. You will be given the option to meet with a registered dietitian in person, via telehealth or by telephone or message through your patient portal at or within a few days of your on-study visit to help plan these meals **(research only)**
- You will be given an intake diary which should be completed daily for the duration of the study **(research only)**

WEEKS 1 & 2 – DIET INTERVENTION GROUP:

- Complete medical history, including any problems you may be having and a list of all medications you are taking (including prescriptions, over the counter medications, herbal medications, and vitamins) **(research only)**
- Limited physical exam including vital signs, weight, and BMI **(research only)**
- Review of adverse events and/or side effects **(research only)**
- Fasting blood work (about 1 teaspoons) will be drawn to check your health **(research only)**
- Waist measurements (Week 2) **(research only)**
- Fasting blood work (about 3 teaspoons) will be drawn to check other health factors like your blood sugar, cholesterol and insulin levels **(research only)**
- During the intake diary review you will be asked about your experiences so far with letrozole and the meal replacement beverage **(research only)**
- Weight and BMI **(research only)**
- Urinalysis **(research only)**
- Questionnaires to see if you are experiencing any stressors or other problems from the diet **(research only)**
- A visit with a registered dietitian in person, via telehealth, or by telephone or patient portal message will be offered during or after your week 1 study visit **(research only)**

ON-STUDY VISIT– LETROZOLE ONLY GROUP:

If you meet all of the screening requirements, you will return to the study clinic for your On-Study Visit. During this visit, you can expect the following procedures to be done:

- Review of medical history and medications since screening **(research only)**
- Physical exam (including vital signs, weight, and height) **(research only)**
- You will take 2.5 mg of letrozole by mouth at the same time every day for the duration of the study (until the day prior to your surgery).
- Fasting blood work (about 1 teaspoon) will be drawn to check your health **(research only)**

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- Waist measurements (**research only**)
- Fasting blood work (about 3 teaspoons) will be drawn to measure additional health factors like your blood sugar, cholesterol and insulin levels (**research only**)
- Urinalysis (**research only**)

WEEK 2 – LETROZOLE ONLY GROUP:

You will be asked to return to the clinic just to obtain blood tests, if possible the day prior to your surgery.

- Fasting blood work (about 3 teaspoons) will be drawn to check other health factors like your blood sugar, cholesterol and insulin levels **(research only)**

FOLLOW-UP:

Safety Follow-Up:

If possible, this visit may occur at the same time as your regularly scheduled post-operative follow-up visit.

- Review of adverse events and/or side effects
- Blood may be drawn if the physician determines it is clinically necessary
- Review of adverse events and/or side effects (you will be followed for up to 30 days following your last dose of letrozole and/or meal replacement)

INSTRUCTIONS WHILE CONSUMING THE MEAL REPLACEMENT BEVERAGE:

- You will be given an intake diary which should be completed every day you are on the study. You will bring this diary with you to all study visits so that the study team can review it.
- You will be asked not to consume any other beverages containing calories besides the shakes. Diet sodas, coffee, and tea will be permitted. You may use calorie-free sweeteners and a limited (Less than 1 tsp/cup) amount of milk or cream in coffee. Sweet tea, energy drinks, milk, and alcoholic beverages will not be permitted.
- You will be asked to write down daily, in your intake diary, how many shakes you had, all food and drinks you had, and if you took your daily Letrozole.

LONG TERM FOLLOW-UP:

You will be followed for health status and BMI for 1 year after surgery at approximately 3-6 month intervals. If you are unable to return to Vanderbilt for follow-up visits, the study team may review your medical chart, contact outside facilities, or contact you by phone or email in order to obtain survival status. At each follow-up, the following will be documented:

- Review of diseasestatus
- Weight
- Health status

Payments for your time spent taking part in this study or expenses:
You will not be paid to participate in this study.

Costs to you if you take part in this study:
If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Brent Rexer, MD, PhD at [redacted]. If you cannot reach the research staff, please page the study doctor at [redacted]

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For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
The study doctor, sponsor, or regulatory authority (FDA, Institutional Review Board, etc.) may choose to end your participation in this study without your consent. This could happen for reasons such as:

- The study doctor feels it is not in your best interest to continue in the study
- You fail to follow the study doctor's instructions
- You experience an adverse reaction that requires other medical treatment
- You become pregnant, or
- The sponsor, or the FDA or other regulatory authority stops the study for any reason

If you are removed from the study, the reason will be explained to you.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Your information and samples will be given a unique code instead of your name to help protect your identity. Dr. Rexer, his staff at Vanderbilt and other authorized people will be the only people who know your personal information. Results of this study may be presented in meetings or in publications. Your identity will not be released in those presentations. Your study records will be secured in the clinical trials office. Your research data will be kept for an unknown period of time. Your tissue and blood samples will be kept in locked storage and may be used or stored indefinitely from the end of the study. Any samples that are not needed will be destroyed.

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Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Rexer and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Results:
Results of your treatment will be shared with you by your study doctor. Results of this study may be presented in meetings or in publications. A summary of results will be available on www.clinicaltrials.gov, as required by U.S. Law.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical

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Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies such as the Food and Drug Administration, National Institutes of Health, National Cancer Institute, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____

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Consent for Sample and Data Storage and Future Research

You are being asked to give any leftover blood and tissue samples for research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

Up to three blood samples, totaling just over one tablespoon, will be drawn from a vein in your arm using a needle. This will not take additional time because it will happen while you are having your blood drawn during your scheduled appointments. Extra biopsy tissue from your diagnostic biopsy and from your surgery will be collected. This will not require any extra time for you. If your surgery is delayed or you decide to continue with additional non-surgical treatment (instead of having surgery) then a breast biopsy may happen. This biopsy will use ultrasound to guide the biopsy if that was used for your initial diagnostic biopsy. This will take around two hours of your time.

Blood samples – You may feel bothered or pained from the needle stick. You may have a bruise or the site may get infected. It is rare, but some people faint.

Biopsy samples – Having a biopsy may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsy. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Rexer and his study staff will have access to your name.

Your samples will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

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Your samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for future research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Brent Rexer or his study staff at [redacted] or in writing. His mailing address is Brent Rexer, MD, PhD. [redacted] to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

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Please check Yes or No to the questions below:

My blood/tissue sample may be used for research.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future research.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature:_____ Date:_____